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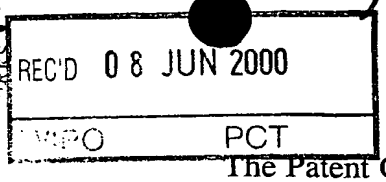

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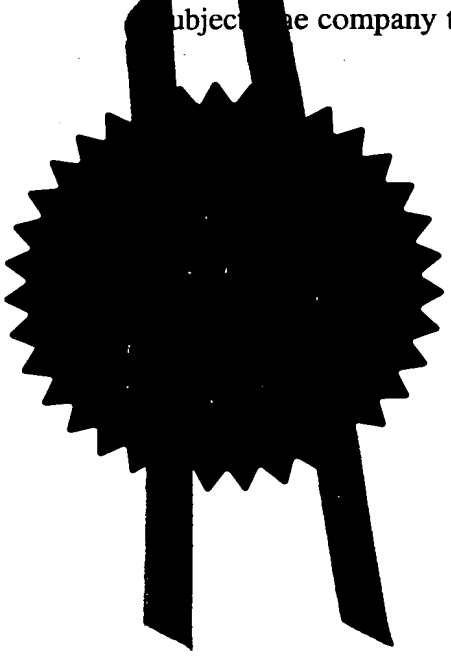

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Dated 25 May 2000

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Request for grant of a patent

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1. Your reference — PHM 99-075/GB/P

2. Patent application number *(The Patent Office will fill in this part)* — 19 MAY 1999 — **9911499.3**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Zeneca Limited
15 Stanhope Gate
London W1Y 6LN
GB

Patents ADP number *(if you know it)* — 6254007002

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention — MEDICAMENT

5. Name of your agent *(if you have one)* — BILL, Kevin

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Intellectual Property Department
ZENECA Pharmaceuticals
Mereside, Alderley Park
Macclesfield, Cheshire
SK10 4TG . GB

Patents ADP number *(if you know it)* — 4469847002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

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9. Enter the number of sheets for any of the following items you are filing with this form.
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Continuation sheets of this form	
Description	5
Claim(s)	2
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Lynda M. Slack Date 18 May 99

12. Name and daytime telephone number of person to contact in the United Kingdom

MRS LYNDA M SLACK - 01625 516173

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Notes

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MEDICAMENT

This invention relates to a method of controlling the weight of patients and is particularly concerned with a method of treating psychoses in patients who are exhibiting diabetes or who at risk from developing diabetes.

It is well recognised that there is a link between obesity and diabetes, especially type II diabetes, and that moderate to severe obesity increases the risk of developing diabetes. It is also widely accepted that weight loss results in metabolic improvement and hence in glycaemic control and insulin sensitivity which in turn give rise to improvements in cardiovascular risk factors. This is reported by, for example, Bosello et al, Int. J. of Obesity, (1997) 21, Suppl 1, S10-13.

In addition to lifestyle factors such as exercise and diet there are other factors which may play have a detrimental effect in weight management. A particular example of these other factors is the weight gain sometimes experienced with certain medication.

It is known that anti-psychotic agents such as clozapine tend to result in patients gaining weight. This in itself is generally undesirable but is more so in patients who are diabetic or who at risk from developing diabetes.

We have now unexpectedly found that 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1.4]thiazepine has properties which means that it is potentially useful in managing the weight of patients. In particular, we have found that, unlike a clozapine, 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1.4]thiazepine has the unusual effect of inducing weight loss.

The compound 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1.4]thiazepine and its use in treating schizophrenia is described in granted European Patent No. EP 240,228.

The term "Agent" referred to hereinafter means 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1.4]thiazepine or a pharmaceutically acceptable salt thereof.

According to the present invention there is provided a method of managing the weight of a patient comprising administering on effective amount of the "Agent" thereof to said patient..

Thus, the present invention also provide the use of the "Agent" for the manufacture of a medicament for managing the weight of a patient.

According to the present invention there is also provided method of treating psychoses in a patient who is diabetic or who is at risk from developing diabetes which method comprises administering an effective amount of the "Agent" to said patient.

Thus, the present invention also provides the use of the "Agent" for the manufacture of a medicament for treating psychoses in a patient who is diabetic or who is at risk from developing diabetes.

In particular the patient is diabetic, that is exhibiting one or more of the symptoms of diabetes.

The "Agent" is particularly effective in inducing weight loss in patients who have tended to gain weight when treated with other antipsychotics such as clozapine. Under such circumstances, the "Agent" may reverse at least part of any weight gained as a result of treatment with the antipsychotic such as clozapine.

The "Agent" may be administered as the compound, 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1.4]thiazepine or may be administered in the form of a pharmaceutically acceptable salt. Examples of suitable salts include, for example, chloride, maleate, fumarate, citrate, phosphate, methane sulphonate and sulphate salts. Preferred salts include fumarates and a particularly preferred salt is the hemi-fumarate.

It is generally preferred that the "Agent" comprises the compound 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1.4]thiazepine in the form of a salt, and in particular a fumarate (2:1) salt.

In the treatment of the diseases mentioned above the "Agent" may be administered orally or parenterally in a conventional dosage form such as tablets, pills, capsules, injectables or the like. The dosage in mg/kg of body weight of the compound used to treat mammals will vary according to the size of the mammal and particularly with respect to the brain/body weight ratio. In general, a higher mg/kg dosage for a small animal such as a dog will have the same effect as a lower mg/kg dosage in an adult human. A minimum effective dosage for the "Agent" will be at least about 1.0 mg/kg of body weight per day for mammals with a maximum dosage for a small mammal such as a dog, of about 200 mg/kg per day.

For humans, a dosage of about 1.0 to 40 mg/kg per day will generally be effective.

Typically, a dosage of about 25mg to 800mg per day will generally be effective. Usually, a dosage of about 150mg to 750mg per day will be administered, with a convenient dosage being about 300mg per day. In some groups of patients a lower dosage may be preferred such as 100mg per day. The dosage can be given once daily or in divided doses, for example, 2 to 4 doses daily. The dose may be conventionally formulated in an oral or parenteral dosage form by compounding 25 to 500 mg per unit dosage of conventional vehicle, excipient, binder, preservative, stabiliser, flavour or the like as called for by accepted pharmaceutical practice, for example, as described in US Patent 3,755,340.

The "Agent" may be used in pharmaceutical compositions as the sole active ingredient or may be contained in a pharmaceutical composition together with one or more other active ingredients, or it may be co-administered with one or more known drugs.

The "Agent" may be administered in conjunction with one or more other agents useful for treating diabetes.

The "Agent" may be administered in conjunction with one or more other agents useful for treating psychoses.

As indicated above, where the "Agent" is administered in conjunction with another agent it may be administered simultaneously, sequentially or separately with that other agent or agents. Thus, as indicated above the "Agent" may be formulated with the other agent or agents or may be presented as a separate formulation.

Thus in one aspect of the present invention there is provided a pharmaceutical composition comprising the "Agent" an agent known for treating diabetes together with a pharmaceutically acceptable diluent or carrier.

In a further aspect there is provided a pharmaceutical composition comprising the "Agent" and an agent for treating diabetes for simultaneous, sequential or separate administration.

The preparation of 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1.4]thiazepine and its pharmaceutically acceptable salts is described in, for example, granted European Patents Nos. EP 240,218; EP 282,236 and in pending

International Patent Application No. PCT/GB98/02260. This compound is commercially available under the generic name quetiapine fumarate.

The invention will now be illustrated with reference to the following, non-limiting examples.

Example 1

Body weight data were collected for a group of 65 randomly-selected schizophrenic patients who were on clozapine initially (200 - 800 mg/day for 6 months) and then had quetiapine added to their therapy. Weights were recorded monthly, and status of diabetes follow-up was also performed. Clozapine dosages were reduced as quetiapine was added. The duration of treatment with quetiapine was 10 months. Data were extracted from retrospective chart review of 65 patients who were prospectively assigned to clozapine-quetiapine therapy. All 65 patients showed weight loss ranging from 0.5 to 23 lbs, with a mean loss of 3.98 lbs, after the first month of combination treatment; the quetiapine dose at one month ranged from 200 - 800 mg/day. The improvement continued throughout the 10-month study period. Total weight loss ranged from 1 to 41 lbs, with a mean loss of 9.2 lbs over the course of the study. Twenty per cent of patients developed diabetes during clozapine monotherapy and each showed significant improvement of diabetes with addition of quetiapine, as assessed through monthly blood monitoring and clinical improvement.

Thus, an unexpected clinical effect of quetiapine is its apparent propensity to induce weight loss and help with diabetes management in patients who gain weight and develop diabetes on clozapine.

Note: quetiapine is 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1,4]thiazepine fumarate (2:1) salt.

Example 2

The following illustrate representative pharmaceutical dosage forms containing the compound 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1,4]thiazepine and salts thereof.

(a) Tablet	mg/tablet
Quetiapine	50.0
Mannitol, USP	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Hydroxypropylmethylcellulose (HPMC),	2.25
Magnesium stearate	3.0

(b) Capsule	
Quetiapine	10.0
Mannitol, USP	488.5
Croscarmellose sodium	15.0
Magnesium stearate	1.5

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

A preferred formulation is that available commercially as quetiapine fumarate from ZENECA Limited.

In formulations comprising a combination of active ingredients the further ingredients may be included in the above formulations.

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Astra Zeneca

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